REMARKS

Applicants submitted Response B on August 23, 2002 in reply to the April 23, 2002 Office Action ("Office Action"). On September 4, 2002 an Advisory Action was mailed stating that Response B was not entered on the basis that several aspects of the amended claims created new issues. As such, Applicants have revised the amendments to the claims to remove the matter which was deemed to create new issues for review.

Claim Rejections - 35 USC § 112, para. 2

Claims 24 and 40 have been amended to include a specific listing of solvents in proper Markush form, and the terms "such as," "and the like," and "including" have been removed from the list of solvents in the claims. In addition, claims 24 and 40 have been amended to distinguish the two solvents used in the crystallization steps as "a water-miscible first organic solvent" and "a second organic solvent." These amendments eliminate any indefiniteness of the original language "having limited miscibility or solubility with water."

Similarly, claims 36, 37, 44, and 44, which depend from claims 24 and 40, have been amended to refer to the organic solvent originally described as "having limited miscibility or solubility with water" as the "second organic solvent," and claims 24 and 40 contain the Markush group of possible solvents for the second solvent, support for which is found in the Specification on p. 7, lines 26-36.

Finally, claims 34-35 and 42-43 are hereby amended to describe a "water-miscible" organic solvent instead of a "water miscible or water-soluble" organic solvent, the terms being synonymous. These amendments make the claims consistent with claims 24 and 40, previously amended in like manner in Response A, from which claims 34-35

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and claims 42 and 43 depend, respectively. Support for these amendments is found in the application, p. 7, lines 6-11.

In light of the above amendments, it is respectfully submitted that the bases for the § 112, para. 1 and 2 rejections have been removed. Applicants respectfully submit that all claims are thus in condition for allowance.

Claim Rejections - 35 USC § 102 (b)

Claims 40-42 and 46 remain rejected under 35 USC § 102(b) as being "clearly anticipated by US 4,319,039 [AB]." (See p.3, second paragraph.)

Applicant has amended claim 40 as suggested by the Examiner, replacing the open-ended phrase "comprise" with the close-ended phrase "consist of" in line 3 of claim 40.

In addition, Applicant re-emphasizes that the presently claimed invention, with two combined crystallization steps, one involving the use of a water-miscible first solvent and the other the use of a second organic solvent selected from the group consisting of butanol, isobutanol, amyl alcohol, hexanol, 2-ethylhexanol, benzyl alcohol, cyclohexanol, methylbutyl ketone, methyl isobutyl ketone, cyclohexanone, methyl acetate, ethyl acetate, n-propyl and isopropyl acetate, t-butyl, isobutyl, sec-butyl acetate, amyl acetate, diethyl ether, diisopropyl ether, methylene chloride, chloroform, acetonitrile, and mixtures of these solvents, as final steps to obtain HMG-CoA reductase inhibitors having a purity higher than 99.6%, is not anticipated by US 4,319,039, Albers-Schonberg et al. The Office Action states that the '039 patent discloses crystallization of the inhibitor from first "a mixture of chloroform/methanol/NH_4OH/ether (water immiscible) ... followed by crystallization from ethanol." See Office Action, p. 4. However, the '039 patent's

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protocol has two alternative pathways for purification of the HMG-CoA reductase inhibitors. The first involves recrystallization of the crude ammonium salt from the chloroform mixture (limited miscibility solvent) (see col. 13, lines 22-28) followed by a final purification from hot isopropanol with 5% concentrated ammonium hydroxide (a second limited miscibility solvent) (see col. 13, lines 61-68).

The alternative purification pathway involves converting the crude ammonium salt to the lactone form using toluene under reflux conditions, (limited miscibility solvent) (see col. 13, lines 29-37), recystallizing the lactone from ethanol (water miscible solvent) (see col. 13, lines 43-45) and then converting the lactone back to the ammonium salt by 1) dissolving the lactone in basic methanol and filtering; 2) evaporating the methanol; 3) redissolving in acidic ethyl acetate; and 4) precipitating with a mixture of chloroform/methanol/concentrated NH_4OH followed with acetone (second limited miscibility solvent) (see col. 13, lines 46-59). The resulting crude ammonium salt product is subjected to final purification by crystallization from hot isopropanol with 5% concentrated ammonium hydroxide (third limited miscibility solvent) (see col. 13, lines 61-68).

Thus, the '039 patent does not disclose combined crystallization steps consisting of only two crystallization steps wherein one involves an organic solvent selected from the above list of solvents, and the other involves a water-miscible organic solvent, as required by amended claims 40-46 in the present application.

In addition, the presently claimed invention results in HMG-CoA reductase inhibitors with greater than 99.6 % purity while maintaining high overall yields (see examples 1, 2, 4 and 5). In contrast, the '039 patent discloses a purification scheme that

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results in greater than or equal to 99 % purity for the lactone (see col. 13, lines 43-45) which is further purified to the ammonium salt form at greater than or equal to 99.5 % purity (see col. 14, lines 1-4). However, there are no results, in fact, evidencing successful purification as high as 99.6 % purity or greater, with concomitant high yields.

Applicants respectfully submit that such high purity, while maintaining high yields, is very difficult to achieve, because of undesired side products having similar structures to the desired inhibitor co-purifying with the desired inhibitor. Therefore, conventional purification schemes such as disclosed in the '039 patent may lead to high purity, but at purities greater than 99.6 % (if attained at all by such methods) the loss in yield is significant.

In summary, Applicants respectfully submit that the '039 patent does not anticipate the presently claimed invention as amended.

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CONCLUSION

Claim 47 has been cancelled, and claims 24, 34-37, 40, and 42- 45 have been amended to eliminate the indefinite terms and the matter which raised new issues for examination. Specifically, in claims 24 and 40, and dependent claims 36, 37, 44, and 45, the two organic solvents disclosed in the two crystallization steps have been distinguished by the terms "water miscible first organic solvent" and "second organic solvent selected from the group consisting of ..." and applicable solvents have been included as a list, for which there is support in the specifications on p. 7, lines 26-36. In addition, the phrase "wherein the limited solubility is in the range of about 0.25 g/ 100 mL and about 30 g/ 100 mL," has been deleted from claim 40 because it was inadvertently and erroneously added in Response A.

With respect to the Office Action, Applicants respectfully submit that claim 40 as amended contains no new matter and is not indefinite. And with respect to the Advisory Action, Applicants respectfully submit that no new issues for review have been raised by the Markush list of solvents included in claims 24 and 40, and no new issues for review have been raised with amended dependent claims 36-37 and 44-45, which now refer to "a second organic solvent" which must come from the specific list of solvents defined in claims 24 and 40.

Also, Applicants respectfully submit that claim 40, as amended to clarify the scope of the combined crystallization steps, (i.e. the steps "consist of" rather than "comprise") is not anticipated by the '039 patent.

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For the reasons set forth above, it is submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

Applicant hereby petitions for a three-month extension of time. Please charge deposit account number 19-4972 the $920 extension fee as well as any additional fees that may be required for the timely consideration of this application. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

Date: October 7, 2002

Respectfully submitted,

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Version with Markings to Show Changes

24. (twice amended) A process for the isolation and purification of HMG-CoA reductase inhibitors from mycelium biomass which comprises:

clarifying a mycelium broth and concentrating the clarified broth to a lower volume,

acidifying [~~of~~] the concentrate to a pH value in the range of 4.5 to 7.5, followed by extracting the HMG-CoA reductase inhibitor with ethyl acetate;

optionally performing lactonization;

crystallizing the HMG-CoA reductase inhibitor from:

i) a water miscible first organic solvent; and

ii) [~~an~~] a second organic solvent selected from the group consisting of butanol, isobutanol, amyl alcohol, hexanol, 2-ethylhexanol, benzyl alcohol, cyclohexanol, methylbutyl ketone, methyl isobutyl ketone, cyclohexanone, methyl acetate, ethyl acetate, n-propyl, isopropyl acetate, t-butyl, isobutyl, sec-butyl acetate, amyl acetate, diethyl ether, diisopropyl ether, methylene chloride, chloroform, acetonitrile, and mixtures of these solvents [~~wherein before crystallization, the inhibitor is dissolved in said organic solvents at a temperature of between about 10 to 40°C~~].

34. (once amended) The process according to claim 24, wherein the water-miscible [~~or water soluble~~] organic solvent used in the crystallization step is acetone or a low alkyl alcohol.

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35. (once amended) The process according to claim 24, wherein the crystallization step from a water-miscible [~~or water-soluble~~] organic solvent comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

36. (twice amended) The process according to claim 24, wherein the crystallization step from [~~an~~] a second organic solvent comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/L, and removing one-third to three-fourth of said organic solvent.

37. (twice amended) The process according to claim 24, wherein the second organic solvent used in the crystallization step is ethyl acetate.

40. (twice amended) A process for the purification of HMG-CoA reductase inhibitors which comprises subjecting the HMG-CoA reductase inhibitor to combined crystallization steps, which [~~comprise~~] consist of crystallization from a water-miscible first organic solvent and crystallization from [~~an~~] a second organic solvent selected from the group consisting of butanol, isobutanol, amyl alcohol, hexanol, 2-ethylhexanol, benzyl alcohol, cyclohexanol, methylbutyl ketone, methyl isobutyl ketone, cyclohexanone, methyl acetate, ethyl acetate, n-propyl and isopropyl acetate, t-butyl, isobutyl, sec-butyl acetate, amyl acetate, diethyl ether, diisopropyl ether, methylene chloride, chloroform, acetonitrile, and mixtures of these solvents, [~~wherein the limited solubility is in the range of about 0.25 g/100 mL and about 30 g/100 mL,~~] as final steps to obtain HMG-CoA reductase inhibitors having a purity higher than 99.6%.

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42. (once amended) The process according to claim 40, wherein acetone or a low alkyl alcohol is used as the water-miscible [~~or water soluble~~] organic solvent.

43. (once amended) The process according to claim 40, wherein the crystallization from a water-miscible [~~or water soluble~~] organic solvent comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

44. (twice amended) The process according to claim 40, wherein said crystallization from [~~an~~] a second organic solvent comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/L, and removing one-third to three-fourth of said organic solvent.

46. (twice amended) The process according to claim 40, wherein ethyl acetate is used as the second organic solvent.

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